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Non-Cryopreserved Peripheral Blood Stem Cells Autotransplants for Hematological Malignancies Can Be Performed Entirely on an Outpatient Basis

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We have prospectively performed peripheral blood stem cell autotransplants in six patients with hematological malignancies on an entirely outpatient basis. Patients were conditioned with high-dose melphalan and received a median of 4.2 × 10^8/kg non-cryopreserved, non-purged mononuclear cells, containing a median of 3.9 × 10^6/kg CD34 + cells. The median time to achieve > 500 granulocytes/μl was 21 days, with a range of 16 to 40, whereas the median time to achieve > 20,000 platelets/μl was 38 days, with a range of 21 to 48. Only three patients were transfused with platelets whereas packed red blood cells were transfused in two. All patients survived 60 days after the autograft and three are alive at 450, 690, and 1,950 days after the autotransplant. One patient was given an allogeneic bone marrow transplant when relapsing after the autotransplant. One patient had to be admitted to the hospital on day +10 because of fever. A median of 6,500.00 USD per patient was calculated as the total cost of each outpatient autotransplant. Since outpatient autologous transplants with non-frozen PBSC are feasible, restrictions to PBSC autotransplant programs may be overcome and costs may be diminished. Am. J. Hematol. 58:161–164, 1998.

Key words: peripheral blood; stem cells; autotransplant; outpatient

INTRODUCTION

Hematopoietic stem cells collected from peripheral-blood (PBSC) have been successfully used to restore bone marrow (BM) function after high-dose chemotherapy [1]. Both chemotherapy and recombinant hemolymphopoietins have been shown to be useful in mobilizing stem cells from the BM to the peripheral blood (PB) [2]. G-CSF is an effective stem cell mobilizing agent, PBSC being useful to restore hematopoiesis after high-dose chemotherapy [3,4]. In 1993 we started an autologous PBSC transplant program [4,5] and in 1996 it was extended to allogeneic transplants [6]. On the other hand, we in Mexico [7] and others in Israel [8] and the United States [9,10] have shown that chemotherapy-induced neutropenia and thrombocytopenia can be safely supported on an outpatient basis provided certain conditions in the patients are fulfilled. Outpatient autologous transplant programs have been developed in the United States [9,10]; in turn, by cutting down the costs of the hematopoietic stem cell transplants, the procedures will be available to a higher number of patients that profit from this therapeutic option [6,11]. We describe here six patients in whom the PBSC autograft was performed entirely on an outpatient basis, using in all cases a single-day conditioning regimen with high-dose intravenous melphalan.

MATERIAL AND METHODS

Patients

Table I shows some of the features of the six autografted patients. All of them had received prior chemo-

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TABLE I. Salient Features of the Patients Included in the Study*

Status number	Age	Sex	Diagnosis	Days after autograft
1	9	F	M3 AML in first remission	A, 1,950
2	56	M	Transformed non-Hodgkin's lymphoma	D, 60
3	46	F	Transformed non-Hodgkin's lymphoma	D, 210
4	8	F	M2 AML in second remission	D, 220
5	12	F	M2 AML in first remission	A, 690
6	33	M	Refractory Hodgkin's disease	A, 450

*AML, acute myelogenous leukemia; A, alive; D, dead.

therapy and had a Karnofsky score of 100% when the procedure was performed. With the exception of patient number two, BM aspiration and biopsy and search for minimal residual disease by means of flow-cytometry were normal or negative [12,13]. In cases 1, 4, and 5, the PML/RARa or the AML1/ETO transcripts were negative as assessed by the polymerase chain reaction [14].

PBSC Mobilization and Apheresis

G-CSF (5 mg/kg/day) was started on day −7 and given until >500 granulocytes/μl were achieved. PBSC mobilization was begun at least 30 days after the last dose of chemotherapy. Using a Majurkar-type subclavian catheter, the apheresis procedures, on an outpatient basis, were performed on days −4, −3, and −2, by means of a Haemonetics V-50 PLUS machine (Haemonetics Corporation, Braintree, MA) and the Spin-Nebraska protocol [15]. The endpoint of collection was processing 5,000 ml of blood/m^2 in each of the three apheresis procedures [5]. The products of the apheresis and 1-ml aliquots were kept in ACD-A (Baxter Healthcare, Deerfield, IL) at 4°C, in 300-ml transfer packs (Baxter Healthcare) composed of gas impermeable, polyvinyl chloride plastic film [5]. The details of the loss of stem cell viability under the conditions of storage used have been published previously [5].

Conditioning and Autografting

High dose intravenous melphalan (HD-MFL, 200 mg/m^2) was delivered along a 30-min period on day −1. Ondansetron (1 mg iv every hour during 4 hr after chemotherapy), ciprofloxacin (250 mg bid), and itraconazole (100 mg bid) were used in all patients; antibiotics and antimycotics were used until granulocytopenia resolved. The products of the PBSC apheresis performed on days −4, −3, and −2 were infused to patients on days 0, +1, and +2, respectively, as outpatients. Patients had laboratory workup and clinical studies performed every day.

Apheresis Products Studies

All apheresis products and their aliquots were kept in a conventional blood bank refrigerator at 4°C and studied at the time of harvesting and at 24, 48, and 72 hr afterwards [5]. Enumeration of the total white blood, mononuclear (MNC) and CD34 positive cells was done by flow-cytometry [16] in an EPICS Elite ESP apparatus (Coulter Electronics, Hialeah, FL), using for the latter subpopulation the anti-CD34 monoclonal antibody HPCA-2 [17] (Becton Dickinson, San Jose, CA), gating in the CD45 (+) MNC population according to forward and 90° angle light scattering [17]. Viability of the MNC cells was assessed by propidium iodide exclusion using flow-cytometry [16]. No purging procedures were performed.

RESULTS

Patients received a median of 4.2×10^8/kg viable MNC in three reinfusions (1.4×10^8 MNC/kg in each reinfusion) containing a median of 0.98% CD34 (+) viable cells in the MNC of the apheresis products, thus making a median of 3.9×10^6/kg CD34 (+) viable MNC (1.3×10^6/kg CD34 + MNC in each reinfusion). There were no febrile episodes nor other side effects of the PBSC reinfusion in any case. Two patients developed mild mucositis and were given acyclovir. The median time to achieve more than 500 granulocytes/μl was 21 days, with a range of 16 to 40, whereas the median time to achieve more than 20,000 platelets/μl without transfusion, was 38 days, with a range of 21 to 48. The patients more heavily pretreated (5 and 6) were the ones that had the longest recovery intervals. We found no relationship between peripheral blood counts and the CD34 cell dose. Only three patients were transfused with platelets, a median of 10 U during the thrombocytopenic period; platelets transfused only of bleeding symptoms were evident. Packed red blood cells were transfused in two patients; red cells were transfused only if clinical symptoms of anemia were present. It should be mentioned that the relatively low intensity of the conditioning regimen could have affected the low transfusion requirements. Patient number one, previously published [14,18], remains in complete remission 60 months after the autograft, despite the fact that the PML/RARa fusion protein was recorded in one of the apheresis products once it had already been reinfused to the patient [14]. Patients 2 and 3 had only partial responses and died 60 and 210 days after the autograft. Patients 4 and 5 had a relapse 220 and 300 days after the autotransplant, the AML1/ETO fusion protein reappearing in both of them. Patient 5 received an allogeneic bone marrow transplant from her HLA-identical sibling and is alive 690 days after diagnosis in hematological and molecular remission. Patient 6 remains in complete remission >450 days after the autotransplant (see Table I). All patients survived 60 days after the autograft and only one (number 6) had to be admitted to the hospital on day +10 because of fever that

resolved after a 48-hr course of cefotaxime. There were no other infectious episodes in the other patients. A median of 6,500 USD per patient was calculated as the total cost of each outpatient autotransplant.

DISCUSSION

Efforts to make the benefits of hematopoietic stem cell transplants acquaintable to a larger number of patients have been manifold [5–6, 9–11, 19]. Grafting PBSC instead of bone marrow stem cells has been shown to be less costly [20]; on the other hand we [4, 5] and others [21–25] have shown that autografts can be performed safely without freezing devices, keeping the stem cells in a conventional blood bank refrigerator, at 4°C, for up to 96 hr. It has also been shown that stem cells can be frozen without controlled cryopreservation [26], that hematopoiesis can be restored using mobilized whole unprocessed blood [27], and that a single, large volume apheresis procedure could be enough to obtain apheresis products capable to reconstitute hematopoiesis after ablative chemotherapy [26]. All these modifications of the autografting procedures have resulted in diminished costs and, accordingly, in availability of the procedure to a larger number of patients: these observations are particularly important in places with limited economic resources [11]. In other outpatient autotransplant programs, chemotherapy is delivered as in-hospitals [9]; in order to be able to perform the autografting entirely on an outpatient basis, we chose high-dose melphalan for this prospective study, since it produces very little mucositis and can be delivered in a single dose.

We have been able to calculate that the previously described outpatient autograft procedures using non-cryopreserved PBSC had an approximate cost of 6,500.00 USD, a figure substantially lower than that reported in the United States for autotransplants [28], and lower than the one that we have also calculated for in-hospital PBSC autotransplants: 7,500.00 USD [5]. Accordingly, cutting down the expenses by abrogating hospitalization is another way to make the stem cell support affordable to patients; in addition, the psychological advantages of the outpatient stay adds to the well-being of the patient and might lead to less severe infections, since hospital-acquired infections are usually more severe than those acquired in the community [7,8]. The outpatient autotransplant program cannot be offered to all patients needing an autograft: Only those asymptomatic, fully active, able to stay in their houses, with relatives or friends or in nearby-hotels, and with a fair educational level can be offered this program. We have been able to perform the outpatient autotransplant program in 6 out of 14 patients that have been autografted. Fundamental to the success of this approach is the availability of a 7-day-a-week clinic where medications and transfusions can be rapidly and efficiently provided for neutropenia or thrombocytopenia during the nadir [9].

The simplification of the autografting methods, envisioned years ago by some experts as turning into outpatient procedures [29,30] is now a reality that most likely will benefit an increasing number of patients with hematological and non-hematological malignancies [9,10,31].

NOTE ADDED IN PROOF

Six more patients have been autografted since the acceptance of the manuscript, using the same protocol and obtaining similar results.

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